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14. ABSTRACT The background fact of this proposal recognizes that estrogen can cause breast cancer in susceptible women, but has beneficial effects elsewhere. Thus, we need to discover better selective estrogen receptor modulators (SERMs). We propose to discover SERMs through the topology of the electron density. Our rationale hypothesizes that topological pharmacophores exist in the molecular electron density as the fundamental identifying characteristics of SERMs. Our specific aim is to find SERM quantum pharmacophores by calculations of the electron density. We propose to compute the following topology characteristics of the molecular electron density: AIL (atomic interaction line), BCP (bond critical point), BP (bond path), CP (critical point), CCP (cage critical point), IAS (inter-atomic surface), (N)NA ((non)nuclear attractor), RCP (ring critical point). Each of the above topological characteristics is uniquely defined by the density, giving it existence at specific geometrical positions in the molecule. Quantum calculation of the electronic density over a drug molecule data base will uncover those topological pharmacophores having geometrical positions & orientations which closely match the cases of known estrogen mimics. This would provide a fundamental new methodology to discover improved SERM drugs, to prevent breast cancer, and promote general health, consonant with National Cancer Institute goals.					
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Final Report: Award Number W81XWH-06-1-0658 **Discovery of Breast Cancer SERM Molecules: Novel use of Fundamental Quantum Mechanics.**

This proposal was concerned with the effects of Estrogen as a cause of breast cancer in susceptible women. The National Cancer Institute has identified a need to discover better selective estrogen receptor modulators (**SERMs**) [1]. It was our concept, to discover SERM molecules through the quantum mechanical topology of the electron density. This is reasonable because of the Hohenberg-Kohn (**HK**) theorem [2], which asserts that all quantum properties of a molecule are **encrypted** within the electron density. Thus, to know the electron density is to know all quantum properties, including the quantum properties which govern the binding of estrogen and SERM molecules. It was our **hypothesis that quantum topological pharmacophores [3] exist in the molecular electron density as the fundamental identifying characteristics of SERM molecules.** Our specific aim was to find SERM quantum pharmacophores by calculations of the electron density. We therefore set out to consider both, the set of possible quantum topological pharmacophores, and also the most efficient ways to calculate accurate electron densities.

Quantum topology [4] presents candidate topological pharmacophores such as: **AIL** (atomic interaction line), **BCP** (bond critical point), **BP** (bond path), **CP** (critical point), **CCP** (cage critical point), **IAS** (inter-atomic surface), **(N)NA** ((non)nuclear attractor), **RCP** (ring critical point). All these candidate pharmacophores were included in our proposal, and were considered by us. But we eventually realized the best topological pharmacophore would likely be the **Laplacian** of the density, $\nabla^2\rho$, as it determines where electronic charge is locally concentrated, $\nabla^2\rho < 0$, and depleted, $\nabla^2\rho > 0$. The physical significance of this is that a SERM and an estrogen receptor must have complimentary Laplacians for an effective bonding interaction to occur between them. That is to say, where the receptor has locally concentrated density a SERM molecule must present a locally depleted density, and vice versa. Because the estrogen receptor is a large biological molecule the calculation of its electron density by abinitio quantum mechanics presents a computational challenge. When it is realized that the estrogen receptor, in bonding combination with many SERM molecules are to be investigated, the computational challenge is even greater. Moreover, such calculations at a variety of quantum chemical levels would be of interest, e.g., HF, DFT, MP2 etcetera. This led us to consider how we could simplify quantum calculations on the one hand, but retain ab-initio accuracy on the other hand.

Our familiarity with the kernel energy method (KEM) [5] made us aware of its usefulness in treating large biological molecules. The essence of the method is that a large biological molecule, too large for convenient calculation, is broken into smaller manageable pieces, called kernels. The energy and density of the full molecule is obtained by certain summations over those of the kernels. Our concern however was the extent to which we could push for highly accurate results. For this reason, we considered the extension of the KEM to a fourth order of interaction among the kernels which compose a biological molecule. The results of extending the KEM to fourth order are highly accurate, as indicated in our publication [6].

The formulas for invoking the KEM up to an order of approximation including quadruple energies may be displayed as

$$E_n^{total} = \left(\sum_{\substack{i=1 \\ i < j < k < l}}^{n-3} E_{ijkl} \right) - (n-4) \left(\sum_{\substack{i=1 \\ i < j < k}}^{n-2} E_{ijk} \right) + \left(\sum_{i=1}^{n-4} i \right) \left(\sum_{\substack{i=1 \\ i < j}}^{n-1} E_{ij} \right) - \left(\sum_{j=1}^{n-4} \sum_{i=1}^j i \right) \left(\sum_{i=1}^n E_i \right)$$

where n is the number of kernels that make up the molecule, and the number of subscripts attached to the symbol for energy E indicate single, double, triple, or quadruple kernels. An indication of the high accuracy obtainable by the KEM extended to a fourth order of interaction is shown in table 1. As the order of the interactions included go from single to double to triple to quadruple, ΔE the difference between the exact answer and the calculated KEM approximation goes toward zero. The calculations in the table are HF, but the same method would apply to other chemical model calculations, e.g., DFT, MP2 etcetera.

Table 1. The Hartree Fock STO-3G energy calculated up to fourth order of KEM, for Leu¹- Zervamicin (closed form) 265 atoms.

Energy	Single	Double	Triple	Quadruple
E_{KEM} in [au]	-5857.8663	-5851.5469	-5851.5686	-5851.5703
E_{exact} in [au]	-5851.5703	-5851.5703	-5851.5703	-5851.5703

ΔE in [au]	6.2960	-0.0234	-0.0017	0.0000
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Thus we now have a way to obtain accurate quantum electron densities for the estrogen receptor alone and in interaction with its SERM molecules. Given the quantum electron density of the estrogen receptor and a SERM molecule, their Laplacian topological characteristics are easily and uniquely defined by that density, giving them existence at specific geometrical positions in the space of the molecules. We have therefore paved the way to use the Laplacian of the electron density as a practical quantum topological pharmacophore. This suggests a fundamental new methodology to discover improved SERM drugs, to prevent breast cancer, and promote general health, consonant with National Cancer Institute goals. Other papers which make reference to Award Number W81XWH-06-1-0658 are references [7,8] .

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